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## HCV infection is independently associated with depression among methadone maintenance treatment heroin users in China

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### Abstract

**Background**—Depression and hepatitis C virus (HCV) infection are two common conditions among heroin users in methadone maintenance treatment (MMT). However, the comorbid relationship between depression and HCV infection among MMT patients is not well understood.

**Methods**—115 MMT patients were recruited from the Yangpu MMT Clinic in Shanghai. Demographic characteristics, drug use and HCV-related information were collected via a structured interview. The Beck Depression Inventory (BDI-II) and the Perceived Stress Scale (PSS) were administered to evaluate participants' symptoms of depression and stress severity. HCV antibody (anti-HCV) test results were collected from patients' MMT clinical medical records.

**Results**—58.2% of participants were anti-HCV positive, and 41.3% scored moderate-to-severe for symptoms of depression (BDI-II scores >19). The prevalence of depressive symptoms (BDI-II score >19) was greater in HCV positive than HCV negative participants (51.6% vs 27.7%, respectively;  $p=0.02$ ). There was no significant difference in the perceived stress level by anti-HCV status; overall the perceived stress level score was  $15.9\pm 5.7$ . In logistic regression analysis, positive anti-HCV status (OR=3.75, 95%CI=1.42–9.90), and greater perceived stress (OR=1.23, 95%CI=1.11–1.36) were independently associated with depression, after controlling for gender, age, duration of drug use and the awareness of HCV infection.

**Conclusion**—Depression and HCV infection are common and co-occurring among MMT patients in Shanghai. HCV infection itself appears to be associated with depressive symptoms regardless of whether the individual is aware of his HCV infection status. This finding indicated that it is important to consider the impact of depressive symptoms on injection risk behaviors and HCV transmission when planning intervention program in MMT clinic.

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## Keywords

depression; hepatitis C; methadone maintenance treatment; perceived stress

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## Introduction

Depression is a common disorder with a lifetime prevalence of about 12–15% in the general population [1]. However, it is ubiquitous among drug users. Heroin dependent patients reported prevalence of lifetime depression ranges between 19%–74.3%, and the current prevalence rates range between 10%–30% [2–7]. Hepatitis C virus (HCV) infection is another common condition among drug users. The U.S. Centers for Disease Control and Prevention (CDC) reported that injection drug use accounts for at least 60% of newly reported hepatitis C virus (HCV) infection cases in the US [8]. A substantial body of evidence also finds that depressive symptoms are common in patients with chronic HCV infection [9–11], most researchers thought these depressive symptoms were due to alpha-interferon treatment [12]. Studies on injection drug users attending methadone maintenance treatment (MMT) have reported high prevalence of HCV infection, ranging from 66.7% to 96% [13–16], and depression ranges from 23% to 67.4% [2, 4, 17–19]. However, the relationship between depression and HCV infection among MMT patients is not well studied.

In this study, we hypothesized that HCV infection would be independently associated with depressive symptoms among MMT patients. As some researchers have reported that the high prevalence of depression in HCV infection patients may be related to the stress of coping with a chronic illness [20, 21], and the patients' awareness of the diagnosis and prognosis [22], we also evaluated these factors among patients in the survey.

## Methods

### Participants and Procedures

Participants were patients attending the Yangpu MMT Clinic in Shanghai, China. During the study period, from April to June 2009, the Yangpu Clinic had about 150 patients who met the National Regulations for entering methadone maintenance treatment in China (i.e., DSM-IV criteria of dependence on multi-self-administrations of heroin for one year or more). Study flyers which included study introduction and contact information of researchers were sent to patients at the MMT clinic, Study procedures were explained in detail to those who expressed interest in participating in the study. Informed consent was obtained by research physicians from Shanghai Mental Health Center.

A structured interview conducted in person by the research physicians after informed consent was obtained, which collected information on participants' demographic characteristics, drug use history and HCV-related information (for example, knowledge of HCV infection). After the face-to-face interview, participants were asked to complete the Beck Depression Inventory (BDI-II) and the Perceived Stress Scale (PSS) themselves.

HCV antibody tests results were obtained from the patients' MMT clinic medical records.

The study protocol was reviewed and approved by the Ethics Committee of the Shanghai Mental Health Center.

## Measurements

The Beck Depression Inventory Revised (BDI-II) [23] was used to assess depression symptoms. The BDI-II is a 21-item (four-point scale) self-administered instrument designed to assess the severity of depression symptoms over the preceding week. Each item is assigned a score of 0–3, with 3 indicating the most severe symptoms. A cumulative score is determined by adding the scores of the individual items. BDI-II cutoff scores were determined by using the guidelines set forth in the Beck Depression Inventory manual [23]. High and low scores were grouped. A BDI-II total score of  $\leq 19$  indicated minimal-to-mild depressive symptoms, and a BDI-II total score of  $>19$  indicated moderate-to-severe depressive symptoms. The BDI-II is a reliable and well-validated measure in screening for depression symptoms in adults with Cronbach's alpha ranging from 0.73 to 0.95, and has been widely used in China [24].

The Perceived Stress Scale (PSS)[25] was used to assess the degree to which participants appraised their daily life as unpredictable, uncontrollable and overwhelming. This stress appraisal scale includes 10 items (e.g., "In the last week, how often have you felt that you were unable to control the important things in your life?"); each item is scored on a 5-point scale, ranging from 0 (never) to 4 (very often). The internal and short-term reliability (coefficient alpha reliability: 0.84; two-day test-retest reliability: 0.85) have been found to be satisfactory [25], and the Chinese version of PSS has been found similar psychometric properties (Wang et al., unpublished).

## Data Analysis

All data was checked for expected ranges, presence of outliers and abnormal values to determine the distribution of variables. T-tests were performed to compare groups on continuous variables, and Chi-square tests were used for categorical variables. Logistic regression analysis was performed to assess factors independently associated with depression (BDI-II total score of  $>19$ ). Statistical significance was reported at p-values of less than 0.05. Statistical analyses were conducted using SPSS for Windows (Version 17.0).

## Results

### Participant characteristics

One hundred fifty two patients received the flyer and 115 (75.7%) patients agreed to participate in and completed this study after all study procedures were explained and written consent was obtained. Participant demographics are listed in Table 1.

BDI-II scores were available for 109 participants, the other 6 participants did not complete this questionnaire. 41.3% (n=45) of these participants reported moderate-to-severe range of depression (BDI-II scores $>19$ ). The average BDI-II score was 17.7 (SD=12.8) and the average PSS score was 15.8(SD=5.7).

Sixty seven participants (58.2%) were found to be anti-HCV positive; 11 (16%) reported knowledge that they had been infected. Five of these had received anti-viral treatment for HCV. The prevalence of depression among HCV positive participants was greater than among HCV negative participants (51.6% vs. 27.7%, respectively;  $p=0.02$ ). There was no significant difference on the perceived stress level between HCV positive and negative patients ( $16.3\pm 5.8$  vs.  $15.6\pm 5.7$  respectively;  $p=0.57$ ).

### Multivariate analyses

In logistic regression analysis, controlling for gender, age, duration of drug use, and awareness of HCV infection status, perceived stress and anti-HCV status were independently associated with reported depressive symptoms (Table 3).

### Discussion

We found a high prevalence of depressive symptomatology in our sample: 41.3% reported moderate-to-severe depression. A significantly higher proportion HCV positive participants reported depressive symptoms than HCV negative participants (51.6% vs 27.7%, respectively). Our logistic regression model indicated that HCV infection is significantly associated with symptoms of depression among the MMT patients, which is consistent with our hypothesis. There are several possible biological explanations for more severe depression among the HCV positive heroin users in our study. First, depression in HCV may relate to a dysregulation of the cytokine network. Loftis et al., found that depressive symptoms in patients with chronic hepatitis C infection are correlated with elevated plasma levels of interleukin-1beta and tumor necrosis factor-alpha [26]. Another explanation is a biological effect of HCV infection on cerebral function [27]. A number of studies indicated that HCV infection may have direct impact on the brain [28]. However, this association may only because anti-HCV status is a marker for some other un-measured variable which is really associated with depression.

Over half (58.2%) of participants in this study, had evidence of HCV exposure, similar to other studies of HCV in IDU in China (61.4%) [29]. While other studies have found higher prevalence(85%) in Chinese MMT populations [14], differences may be due to younger age (39 vs 49 years) and shorter duration of drug use (8.7 vs. 17 years) in our study compared to others. In general our findings are consistent with high HCV prevalence globally among populations with a history of injecting[30]. However, less than 20% of the HCV positive individuals understood their HCV infection status, and fewer patients received anti-viral treatment. HCV infection can cause serious health problems and significantly impact the quality of life of methadone maintenance patients [17]. Thus, in the future, the clinicians of MMT clinics must take this into account when providing intervention to this sub-population in China.

Some researchers believe that the stress of coping with a chronic illness [20, 21], i.e., the patients' awareness of the HCV diagnosis and prognosis [22] may contribute to depression. In our study, we did not find the awareness of HCV infection status to be associated with depression. Although the perceived stress was significantly associated with depression in our logistic regression model, there is no significant difference on the perceived stress level

between HCV positive and negative participants. So, although stress is an important risk factor of depression, it is not appear to be a confounding factor between HCV and depression. Thus, HCV infection is associated with depression, independently from perceived stress in this population.

There are several limitations that should be noted. First, this study is cross-sectional so we cannot assess temporality or directionality of the association between depression and HCV infection. Secondly, our measure of HCV infection is imprecise. We did not have information on HCV viremia in this population. So this association may be in fact confounded, with anti-HCV status as a marker for some other un-measured variable. Thirdly, we did not collect medication history among participant in the present study and thus were unable to control for other medications or drugs in our analysis. If any of these factors were non-differentially associated with HCV status, the association between HCV and depression could be biased. We did know that only five participants had received HCV antiviral therapy including with alpha-interferon which is known to induce or exacerbate depression [12, 31, 32]. Finally the sample size for this study was modest, and recruited using convenience methods, so may not be representative of all MMT patients in China. Further studies need to recruit a bigger sample with more diverse background to confirm our findings.

Despite these limitations, our findings have implications for improving intervention programs offered at MMT clinics. This study indicated that HCV infection is significant associated with depression among MMT participants. We understand that the severity of reported symptomatology is associated with a greater frequency of injection risk behaviors among depressed IDUs [33]. In another words, depressed HCV positive IDUs may have more injection risk behaviors which may increase the risk for HCV transmission. Even for those in treatment HCV positive IDUs still at risk of infecting others because of depression. To prevent HCV transmission, it may be advisable to seek treatment for depressive symptoms besides seeking treatment for HCV infection itself among HCV positive heroin users. However, compared with HCV negative patients, less than half of HCV positive patients likely have a regular source of medical care for the diagnosis and treatment of depression [34]. Together, it is very important to consider the impact of depressive symptoms on injection risk behaviors, HCV transmission and HCV treatment seeking behavior when planning intervention program or making related policy, and it is especially important for modifying MMT clinical algorithms.

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**Table 1**

Selected Socio-demographic Characteristics of MMT Patients surveyed and associations with exposure to HCV (anti-HCV positive).

Variables	Total	Anti-HCV positive	OR (95% CI)	P Value
Total N	115	67		
Gender N (%)				
<i>Male</i>	87 (75.7%)	52 (59.8%)	1	
<i>Female</i>	28 (24.3%)	15 (53.6%)	0.87 (0.36–2.07)	0.75
Age (in years)				
Mean (sd)	39.7 (8.7)	40.9 (8.4)	1.04 (0.99–1.09)	0.09
Median(IQR)	39 (32–48)	41 (34–49)		
Marital Status				
Married	25 (21.7%)	14 (56.0%)	1	
Widowed/Separated/divorced	42 (36.5%)	25 (59.5%)	1.16 (0.42–3.15)	0.78
Never Married	48 (41.7%)	28 (58.3%)	1.10 (0.41–2.92)	0.85
Employment				
Employed	28 (24.3%)	16 (57.1%)	1	
Unemployed	87(75.7%)	51 (58.6%)	1.06 (0.45–2.52)	0.89
Education Years (in years)				
Mean (sd)	10.5(1.9)	10.4 (1.8)	0.90(0.74–1.09)	0.28
Median(IQR)	9 (9–12)	9 (9–12)		
Age of first drug use (in years)				
Mean (sd)	28.2(8.7)	28.5 (7.6)	1.01(0.97–1.05)	0.67
Median(IQR)	27 (21–35)	28 (21–35)		
Years of drug use				
Mean (sd)	8.7(3.7)	8.9 (3.3)	1.04(0.94–1.15)	0.49
Median(IQR)	9 (6–12)	9 (6–11)		



**Table 2**

Summary of Logistic Regression Analysis for Variable Predicting Depression

	Odds Ratio(95%CI)	p-value
Gender (male vs. female)	0.78(0.27–2.25)	0.64
Age (in years)	1.02(0.96–1.08)	0.70
Education (in years)	1.57(0.84–2.95)	0.58
Duration of drug use (in years)	1.05(0.92–1.20)	0.16
HCV infection Awareness (yes vs. no)	2.47(0.53–11.39)	0.46
Perceived stress (PSS score)	1.23(1.11–1.36)	<0.001
Anti-HCV status (positive vs. negative)	3.75(1.42–9.90)	0.007

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